Retrospective Review of Genetic Mutations and Treatments in Patients with Monogenic Diabetes of the Youth (MODY)

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Introduction

- Monogenic Diabetes of the Youth (MODY):
- diverse group of genetic disorders that result in diabetes mellitus
  - Account for 1-5% of the pediatric population with diabetes
- 14 genes identified with MODY to date:
  - APPL1, ABCC8, BLK, CEL, GCK, HNF1A, HNF4A, HNF1B, INS, KCNJ11, KLF11, NEURO1, PAX4, PDX1
  - Mutations in these genes can lead to:
    - Insulin secretion defects
    - Glucose sensing defects
    - Beta cell dysfuction

- Identifying MODY:
  - Presentation of diabetes before age 24 years
  - No islet cell autoimmunity
  - Still retain some residual pancreatic function

Methods

- Parameters: all patient seen at Cincinnati Children's Hospital Medical Center (CCHMC) from 2010 – April 2023
- Patient information was de-identified

- EPIC Slicer Dicer to identify MODY diagnoses codes, gene diagnoses codes, and testing results
- Review resulting patient population and the genetic testing results
- Patient population with MODY obtained

- Exclusion criteria:
  - Patients without confirmed genetic testing
  - Patients with reported genetic testing but no test result available in chart review
- Genetic mutations were catalogued
- Demographics for each patient with MODY were recorded
- Time from initial diabetes diagnosis to diagnosis of MODY was calculated for each patient, along with HgbA1c/BMI at diagnosis
- Diabetes co-morbidities for each patient were investigated
- Medications for each patient and genetic mutation were compared

Results

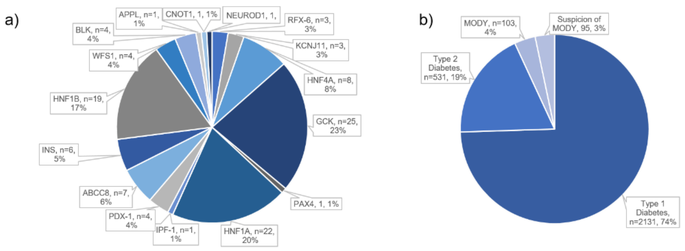

Figure 1. a) Genetic mutations by percentage of the population with MODY. **b)** Population at CCHMC with diabetes by type of diabetes

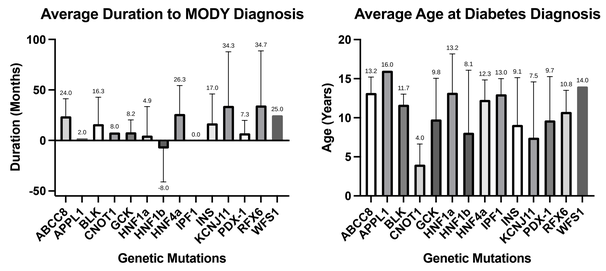

Figure 2: Comparison of time to diagnosis along with demographics at diabetes diagnosis. Notably, patients with a mutation in HNF1b were diagnosed earlier and at a younger age than almost all the other mutations.

Table 1. Characteristics of All Patients at Diabetes Diagnosis and Treatment at Diagnosis

	n	Percent	Mean	SD
Age of Diabetes Diagnosis (years)	104		16.74	16.40
BMI At Diabetes Diagnosis (m/kg^2)	104		0.00	0.00
HgbA1c At Diabetes Diagnosis (%)	104		0.00	0.00
Sex	95			
Female	59	56.73%		
Male	46	44.23%		
Race	104			
White (non-Hispanic)	69	66.35%		
White (Hispanic)	11	10.58%		
Black	18	17.31%		
Asian/Pacific Islander	3	2.88%		
Unknown	3	2.88%		
Islet Cell Autoantibody Screen	104			
Positive	7	6.73%		
Negative	64	61.54%		
Not obtained	33	31.73%		
Initial Diagnosis	97			
Type 1 DM	36	37.11%		
Type 2 DM	7	7.22%		
Beta cell mismatch hypoglycemia	1	1.03%		
Neonatal diabetes	1	1.03%		
MODY	28	28.87%		
Agenesis of the pancreas	2	2.06%		
Unknown Diabetes Type	22	22.68%		
Initial Therapy	98			
Insulin Alone	35	35.71%		
MDI	34			
70/30 Insulin	1			
Metformin	7	7.14%		
Sulfonylurea	1	1.02%		
Insulin and Metformin	3	3.06%		
None	52	53.06%		

Table 2. Co-morbidities of All Patients at Diabetes Diagnosis

	n	Percent
Blood Pressure	77	
Normal	65	84.42%
Hypertensive (mild to Stage I)	12	15.58%
Acanthosis	101	
Present	15	14.85%
Absent	86	85.15%
Ketoacidosis At Diagnosis	101	
Present	7	6.93%
Absent	94	93.07%
Lipid Profile	104	
Normal	47	45.19%
Abnormal	22	21.15%
Not obtained	35	33.65%
TSH	104	
Normal	66	63.46%
Abnormal	5	4.81%
Not obtained	33	31.73%
Celiac Screening	98	
Negative	42	42.86%
Positive	0	0.00%
Not obtained	56	57.14%

Table 3. Medication comparison within the population with MODY.

Current Therapy	n	Percent	BMI Change At Follow-up (kg/m^2)	% BMI Change At Follow-up	HgbA1c Change At Follow-up (%)	% HgbA1c Change At Follow-up
Insulin Alone	18	20.00%	1.32	7.50%	-2.79	-22.38%
MDI Basal/Bolus	10					
Pump Basal/Bolus	5					
MDI Basal Only	2					
Split/Mixed insulin (NPH+regular)	1					
Metformin Alone	4	4.44%	-0.72	-2.46%	-0.05	-0.31%
Sulfonylurea	14	15.56%	-0.61	-2.17%	-0.89	-9.96%
GLP-1 Receptor Agonist	4	4.44%	-1.39	-4.99%	-1.17	-16.10%
Metformin-Glyburide	1	1.11%	2.51	9.94%	-6.00	-42.86%
Insulin and Metformin	3	3.33%	-1.98	-6.40%	-4.50	-38.28%
None	46	51.11%				

Discussion

- The distribution of MODY gene mutations in the population at CCHMC overall reflects that of the more common mutations (HNF1A, HNF4B, GCK)
- A moderate portion of patients with HNF1B mutations were diagnosed at a young age with a very short interval between diagnosis of MODY and diabetes. This could likely be due to the other systemic symptoms such as the presence of renal cysts (detected on prenatal ultrasounds or later in life.)
- Several patients with MODY had DKA. Thus, DKA should not be used to exclude the possible diagnosis of MODY.
- A majority of the patient with MODY did not have the commonly associated co-morbidities seen with T2DM or T1DM.
- Patients treated with insulin alone had great reduction in HgbA1c at follow-up but also had associated weight gain.
- Patients treated with GLP-1 receptor agonists had a smaller reduction in HgbA1c but also had additional effects of reduction in BMI.

Conclusion

Our study highlights the importance of genetic testing in patients as DKA and islet cell antibody positivity (if other than insulin) does not preclude MODY diagnosis. Timely diagnosis of MODY could lead to more targeted therapy. Moreover, future investigation of GLP-1 receptor agonist as a treatment for MODY patients is warranted.

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